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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/719,336	03/22/2001	Mangus Von Knebel-Doeberitz	4121-121	7154

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EXAMINER
QIAN, CELINE X

ART UNIT	PAPER NUMBER
1636	17

DATE MAILED: 09/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/719,336	VON KNEBEL-DOEBERITZ ET AL.	
	Examiner	Art Unit	
	Celine X Qian	1636	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 June 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11 and 13-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11, 13-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *3/22/01* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-11 and 13-15 are pending in the application.

This Office Action is in response to the Amendment filed on 6/27/03.

Response to Amendment

The rejection of claims 1-11 and 13-15 under 35 U.S.C.112 1st paragraph is maintained for reasons set forth of the record mailed on 1/28/03 and further discussed below.

Response to Arguments

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11 and 13-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for lowering chemotherapy resistance in a patient being treated with a chemotherapeutic agent for a small cell lung cancer or pancreatic cancer, the method comprising administering an effective amount of AAV-2 intratumorally in combination of a chemotherapeutic agent to the patient; and determine whether the chemotherapeutic resistance to the chemotherapeutic agent is lowered; a pharmaceutical composition containing a chemotherapeutic agent and an effective dose of AAV-2 to lower resistance of tumor cells to said chemotherapeutic agent in a patient suffering from a small cell lung cancer or pancreatic cancer when it is administered intratumorally; a method for enhancing chemosensitivity of tumor cells to a chemotherapeutic agent, the method comprising administering a sufficient amount of AAV-2 intratumorally in combination with said

chemotherapeutic agent, and determine whether the tumor growth is reduced, wherein the tumor cells are selected from small cell lung cancer or pancreatic cancer; does not reasonably provide enablement for the claimed method and pharmaceutical composition wherein the AAV-2 is administered by any routes, or wherein the tumor cells are from any type of cancer. Further, the specification fails to support a pharmaceutical composition comprising a chemotherapeutic agent and AAV-2 that can completely reverse chemotherapy-induced resistance in patients suffering from any type of cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In response to the enablement rejection, Applicants argue that the claimed invention is not related to gene therapy. Applicants further argue that the AAV-2 virus is used as an infectious agent so that the virus can be introduced to a mammal's system by multiple routes including oral and subcutaneous administration. Applicants finally assert in a Declaration that the cells used in the experiment described in a previous Declaration is isolated from a primary pancreatic tumor, therefore, they represent chemotherapy resistant tumor cells. Applicants thus conclude that the invention is enabled to its full scope by the instant specification.

Applicants' arguments has been fully considered and deemed partially persuasive. The claimed invention is enabled for a method for lowering chemotherapy resistance in a patient being treated with a chemotherapeutic agent for a small cell lung cancer or pancreatic cancer, the method comprising administering an effective amount of AAV-2 intratumorally in combination of a chemotherapeutic agent to the patient; and determine whether the chemotherapeutic resistance to the chemotherapeutic agent is lowered; a pharmaceutical composition containing a

chemotherapeutic agent and an effective dose of AAV-2 to lower resistance of tumor cells to said chemotherapeutic agent in a patient suffering from a small cell lung cancer or pancreatic cancer when it is administered intratumorally; a method for enhancing chemosensitivity of tumor cells to a chemotherapeutic agent, the method comprising administering a sufficient amount of AAV-2 intratumorally in combination with said chemotherapeutic agent, and determine whether the tumor growth is reduced, wherein the tumor cells are selected from small cell lung cancer or pancreatic cancer. However, the instant specification does not support the enablement for the claimed method and pharmaceutical composition wherein the AAV-2 is administered by any routes, or wherein the tumor cells are from any type of cancer. Further, the specification fails to support a pharmaceutical composition comprising a chemotherapeutic agent and AAV-2 that can completely reverse chemotherapy-induced resistance in patients suffering from any type of cancer.

The reasons for the non-enablement rejection were discussed in detail in the previous office action mailed on 6/27/03. Although the claimed invention does not use the AAV-2 virus as a vector to delivery a therapeutic gene, the AAV-2 virus is used as an immuno-sensitizing agent to potentiate the cytotoxic response of a chemotherapeutic agent to a specific type of tumor (small cell lung cancer and pancreatic cancer). This is different from general viral infection in which a number of routes of infection can be achieved. The specification and the Declaration only disclose intratumoral injection of the virus in the method of sensitizing tumor cells to the chemotherapeutic agents. Whether infection of the AAV-2 virus by any other routes would achieve the sensitizing effect is unpredictable. In addition, the tumor in a patient would localize in a particular tissue (depending on the specific type of tumor) rather than at the surface as result

from injection of tumor cells demonstrated by the specification. Certain type of tumors that located at less vascularized tissues may be especially hard to reach. As such, whether a general AAV-2 infection by routes such as oral, subcutaneous would result in the same sensitizing effect of a chemotherapeutic agent as that is disclosed in the specification is unpredictable. Therefore, the invention is only enabled for intratumorally administration of the AAV-2 virus.

The specification also fails to enable a method of sensitizing any type of tumor cells to a chemotherapeutic agent by administering AAV-2 virus. The art teaches that tumors from different origin behave differently toward an anti-tumor agent due to their different intrinsic molecular mechanisms. There is no single anti-tumor agent that is effective against any type of tumors. The specification discloses that even tumor cells isolated from same type of tumor (small cell lung cancer) behave differently toward the chemotherapeutic agent and sensitizing effect of the AAV-2 virus (see table 1 and 2). As such, whether AAV-2 virus can sensitize any type of tumor to a chemotherapeutic agent is unpredictable. Therefore, the specification only supports the enablement for the claimed method and pharmaceutical composition toward small cell lung cancer and pancreatic cancer.

Lastly, the specification fails to demonstrate that AAV-2 virus can completely reverse the chemotherapy-induced resistance of the tumor cells. As discussed in the previous office action, the specification and the Declaration do not teach that the resistance of the tumor cells toward chemotherapeutic agents are induced by said chemotherapeutic agents. Therefore, claims 7-9 are only enabled for a pharmaceutical composition containing a chemotherapeutic agent and an effective dose of AAV-2 to sensitizing the tumor cells or reduce the resistance of the tumor cells

to said chemotherapeutic agents, wherein the tumor cells are pancreatic tumor or small cell lung cancer tumor.

For reasons discussed in previous office action and above, the specification fails to enable the claimed invention to its full scope. One of ordinary skill of art would have to engage in undue experimentation to practice the claimed invention.

New Grounds of Rejection Necessitated by Applicants' Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 13-15 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: whereby a reduction in tumor growth indicates the chemosensitivity of cancer tumor cells is enhanced.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 703-305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Celine Qian, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER